Cariprazine as a maintenance treatment in dual schizophrenia: a 6-month observational study in patients with schizophrenia and cannabis use disorder

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Schizophrenia is often associated with substance use disorders, particularly cannabis use disorder (CUD). However, treatments frequently fail to address both conditions simultaneously. This study aimed to evaluate the antipsychotic effectiveness of cariprazine in patients with both schizophrenia and CUD in a real-world setting. A 6-month observational study was conducted on 58 patients diagnosed with schizophrenia and CUD, treated with cariprazine. Antipsychotic effectiveness was measured using the Positive and Negative Syndrome Scale and the Clinical Global Impression-Schizophrenia Scale, along with the Improvement and Severity scales. Cannabis consumption and addiction severity were assessed using the Cannabis Abuse Screening Test and the Severity of Dependence Scale, while functioning was evaluated with the Sheehan Disability Inventory. Cariprazine treatment resulted in significant improvements in schizophrenia symptoms (Positive and Negative Syndrome Scale change: −47.88 points, $P < 0.0001$; Clinical Global Impression-Schizophrenia Scale change: −8.26 points, $P < 0.0001$). Cannabis use and dependence also decreased (Cannabis Abuse Screening Test change: −7.0 points, $P < 0.0001$; Severity of Dependence Scale change: −7.88 points, $P < 0.0001$), alongside improvements in functioning (Sheehan Disability Inventory change: −9.48 points, $P < 0.0001$). These results suggest that cariprazine is effective for both schizophrenia and CUD, though further research is needed to confirm these findings. *Int Clin Psychopharmacol* **40: 167–175**

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Introduction

Schizophrenia is a complex and multifaceted disorder which often manifests alongside other mental health conditions, including substance use disorder (SUD). The co-occurrence of a SUD and another mental illness – in this case, schizophrenia – is referred to as dual disorder. Schizophrenia patients are up to three times more likely to develop SUD than the general population (Grunze, 2023), and the prevalence of SUD increases as the severity of the another mental disorder does (Szerman *et al*., 2022). The most commonly abused substances among schizophrenia patients include tobacco (32–92%), alcohol (20–60%), cannabis (12–42%), and cocaine (15–50%) (Azorin *et al*., 2016; Khokhar, Dwiel, *et al*., 2018).

Both schizophrenia and SUD have detrimental impact on patients' lives, but their co-occurrence complicates the clinical picture even further: the risk of relapse, rehospitalization, and suicide increases; treatment noncompliance increases; patients experience poorer global functioning and clinical exacerbation; and overall, patients have a worse prognostic outcome (Azorin *et al*., 2016; Khokhar, Dwiel, *et al*., 2018). Therefore, given the high prevalence and the detrimental clinical outcomes of dual disorders, the adequate understanding and management of this condition is of utmost importance.

Cannabis use among schizophrenia patients

The relationship between cannabis use disorder (CUD) and schizophrenia is intricate. Cannabis use rates among schizophrenia patients vary widely, ranging between 17 and 80%. Moreover, the prevalence of CUD is alarmingly high, with estimates fluctuating between 13 and 50% (Volkow, 2009; Koskinen *et al*., 2010; Hunt *et al*., 2018).

The high prevalence and the link between CUD and schizophrenia is in part attributable to a shared genetic basis: studies have shown that people with a higher genetic vulnerability to schizophrenia were more likely to start using cannabis, to use it on a regular basis, and to consume larger quantities of cannabis throughout their lives (Verweij *et al*., 2017).

Emerging evidence links cannabis consumption to an elevated risk of developing psychotic symptoms or disorders – any history of cannabis use is linked to a 1.4-fold increased risk of developing psychotic illness, while CUD is associated with a 3.4-fold increased risk (Hasan *et al*., 2020). Furthermore, cannabis use has been associated with early onset of psychotic symptoms, increased relapse rates, and other complications like lower medication adherence and higher treatment failure rates (Potvin *et al*., 2006; Kuepper *et al*., 2011; García *et al*., 2016; Patel *et al*., 2016; Foglia *et al*., 2017; Schoeler *et al*., 2017; Hasan *et al*., 2020; Volkow *et al*., 2020).

Treatment of schizophrenia and cannabis use disorder

Despite the prevalent co-occurrence of schizophrenia and CUD and their intertwined clinical implications, clinical trials evaluating treatments for schizophrenia frequently do not include individuals with substance use disorders, and trials aimed at treating substance use disorders often exclude patients with schizophrenia (Schultz *et al*., 1997). Furthermore, current treatment guidelines also often overlook the intricacies of dual disorders. A combination of second-generation antipsychotics and psychosocial interventions is the standard recommendation. However, this approach often falls short, overlooking the nuanced neurobiological interplay between addiction and other severe mental disorders (Crockford & Addington, 2017; Szerman & Peris, 2018; Reid & Bhattacharyya, 2019; Alsuhaibani *et al*., 2021; Peris & Szerman, 2021).

Regarding evidence on antipsychotics, a pilot trial suggested a decrease in cannabis use among individuals with schizophrenia who were prescribed clozapine (Brunette *et al*., 2011; Grunze, 2023). However, the outcomes of a confirmatory study (registered under linicalTrials.gov ID NCT01639872) have not been published yet (Khokhar, Henricks, *et al*., 2018; Grunze, 2023). Furthermore, a single randomized comparative study documented a decrease in substance use, predominantly involving alcohol, cocaine, and cannabis, among individuals with schizophrenia who were administered aripiprazole and paliperidone long-acting injectable (Cuomo *et al*., 2018; Grunze, 2023). In addition, in a small-scale trial comparing the effectiveness of olanzapine versus risperidone in reducing cannabis use among individuals with schizophrenia, there was no significant distinction between the two groups in the medium-term follow-up period (n = 28, 1 randomized controlled trial, risk ratio: 0.50, 95% CI: 0.19–1.29, moderate quality evidence) (Pushpa-Rajah *et al*., 2015).

The emergence of partial agonists offers a beacon of hope in this complex landscape: medications with partial agonism for dopamine receptors have been explored as potential treatments for patients with comorbid psychosis and SUDs in recent decades. Partial agonists exhibit unique properties, acting as agonists in the absence of competing molecules but as antagonists when higher intrinsic activity agonists are present, thereby blocking receptor access (Grunze, 2023). This pharmacological mechanism offers improved tolerability compared to pure dopaminergic antagonists, which is a significant advantage. Additionally, partial agonists exert less disruption on neuronal functionality by normalizing and stabilizing neurotransmission tone (Grunze, 2023). Therefore, a dopamine receptor partial agonist could serve as a dopamine stabilizer, enhancing dopaminergic activity in the frontal cortex while reducing hyperactivity in subcortical regions (Grunze, 2023). These molecules, like aripiprazole, have shown promising results in treating dual disorders cases, opening new avenues for therapeutic interventions (Szerman *et al*., 2020; Peris & Szerman, 2021).

Cariprazine

Cariprazine is a novel partial agonist antipsychotic with a unique pharmacological profile. It acts as a partial agonist of dopamine D3 and D2 receptors and has implications on serotonin receptors (Kiss *et al*., 2010). It is indicated for the treatment of schizophrenia (European Medicines Agency, 2017), bipolar disorders (FDA, 2022), or major depressive disorder as adjunctive treatment (FDA, 2022).

Regarding the effectiveness of cariprazine in SUD, available data is primarily derived from animal studies and case reports. One such animal model explored the anti-addiction properties of cariprazine, aripiprazole, and bifeprunox in cocaine addiction in rats (Román *et al*., 2013). All three compounds demonstrated efficacy in reducing the rewarding effects of cocaine, as evidenced by decreased self-administration of the drug. Additionally, they effectively prevented relapse to cocaine-seeking behavior following a period of abstinence from cocaine and its associated cues (Román *et al*., 2013). Cariprazine and bifeprunox exhibited equipotent effects, which were approximately 20 times more potent than those of aripiprazole (Román *et al*., 2013).

In addition to animal studies, there are some case reports documenting the effectiveness of cariprazine in various comorbid SUDs, including cannabis (Montes *et al*., 2021; Rodriguez Cruz *et al*., 2021; Gentile *et al*., 2022), methamphetamine (Montes *et al*., 2021; Ricci *et al*., 2021; Truong & Li, 2022; Moran *et al*., 2023), cocaine (Carmassi *et al*., 2019), and alcohol (Carmassi *et al*., 2019; Halaris & Wuest, 2019). Evidence shows improvements in symptoms of psychotic disorders (positive, negative, cognitive symptoms), psychosocial functioning, and of importance, many patients achieved complete abstinence from the abused substance as a result of cariprazine treatment.

Cariprazine's potential benefits extending to addiction treatment is likely attributable to its high affinity for and preferential binding to dopamine D3 receptors, which play a pivotal role in cognitive, emotional, and reward-related behaviors (Kiss *et al.*, 2010; Leggio *et al.*, 2013, 2016; Cortés *et al.*, 2016). In the context of dual disorders treatment, the partial agonism effect of cariprazine along with its preferential binding to the D3 receptors provide a potential therapeutic avenue, warranting comprehensive exploration and clinical consideration.

Aim

The aim of this study was to investigate the effects of cariprazine in patients with comorbid schizophrenia and CUD in terms of improvement in both schizophrenia symptom severity and cannabis use.

Methods

Study design

This was a 6-month, multicentric, observational study conducted at six Spanish institutions (Gregorio Marañón University Hospital in Madrid, Vall d'Hebron University Hospital in Barcelona, Dr. Peset University Hospital in Valencia, Institute for Addictions in Madrid, Institute of Neuropsychiatry & Addictions-Parc De Salut Mar in Barcelona, and University Healthcare Complex of Salamanca in Salamanca). It received ethics approval by the Ethics Research Committee at the Gregorio Marañón University Hospital in Madrid (FPD-CAR-2021-01) and informed written consent was obtained from all participants. The guidelines set by the Declaration of Helsinki were followed. The study was conducted between June 2021 and November 2022, and consisted of a 6-month examination period by patient, with three evaluation points: at baseline (visit 1), and after 3 and 6 months (visits 2 and 3, respectively).

Patient characteristics

Adult patients aged 18–65 years, with the diagnosis of schizophrenia and CUD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria (American Psychiatric Association, 2013), receiving cariprazine treatment based on medical judgment were included. Additionally, patients with schizophrenia must have been eligible for cariprazine treatment according to its Summary of Product Characteristics (European Medicines Agency, 2024) (meaning all patients except for those with concomitant administration of strong CYP3A4 inhibitors, concomitant administration of strong or moderate CYP3A4 inducers, or pregnancy). Comorbidities that would have confounded the results [incl. additional psychiatric disorders (according to DSM-5), severe liver failure, gastro-intestinal disorders influencing absorption or secretion, etc.] were exclusionary. Patients did however self-report using other illegal substances, which did not fulfill DSM-5 criteria for substance use disorder and were hence not exclusionary. Concomitant medication with centrally active substances was allowed.

Measures

The study assessed change in schizophrenia symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.*, 1990) and the Clinical Global Impression-Schizophrenia (CGI-SCH) (Haro *et al.*, 2003) along with change in CUD symptoms based on the Cannabis Abuse Screening Test (CAST) (Cuenca-Royo *et al.*, 2012; Fernandez-Artamendi *et al.*, 2012) and the Severity of Dependence Scale (SDS) (Castillo *et al.*, 2010; Cuenca-Royo *et al.*, 2012). Additional efficacy measures included the Clinical Global Impression-Severity (CGI-S) and Improvement (CGI-I) Scales (Busner & Targum, 2007), as well as the Sheehan Disability Inventory (SDI) (Bobes *et al.*, 1999). No urine drug analyses were performed to assess change in substance use. All scales were administered at treatment start, at 3 months of treatment and 6 months of treatment (except for the CGI-I scale which was only administered at 3 months and 6 months).

Positive and Negative Syndrome Scale

The PANSS is an assessment tool used to measure the severity of symptoms in patients with schizophrenia. Developed by Kay *et al.* (Kay *et al.*, 1990), the PANSS evaluates both positive (PANSS-P), and negative symptoms (PANSS-N), as well as general psychopathology (PANSS-GP) associated with schizophrenia. It contains 30 single items, each to be rated on a scale of 1–7 points. It is administered by the treating physician.

Clinical Global Impression-Schizophrenia scale

The CGI-SCH scale is designed to assess positive, negative, depressive, cognitive, and overall symptoms in individuals with schizophrenia (Haro *et al.*, 2003). Adapted from the Clinical Global Impression Scale (CGI) and the CGI-Bipolar Patients Scale (CGI-BP), the CGI-SCH consists of 10 items (Haro *et al.*, 2003). Each item is evaluated using a seven-point ordinal scale (Haro *et al.*, 2003). The CGI-SCH provides valuable insights into symptom severity and treatment response in schizophrenia, making it suitable for both observational studies and routine clinical practice (Haro *et al.*, 2003).

Cannabis Abuse Screening Test

The CAST is a widely used self-assessment tool designed to identify patterns of cannabis use that may have negative health or social consequences for both the user and others involved (Cuenca-Royo *et al.*, 2012; Fernandez-Artamendi *et al.*, 2012). The test consists of a series of questions that assess the frequency of cannabis-related behaviors and events over the past 12 months, such as smoking cannabis before midday, smoking alone,

experiencing memory problems after use, and being encouraged by friends or family to reduce consumption (Cuenca-Royo *et al*., 2012; Fernandez-Artamendi *et al*., 2012). Items are rated on a 5-point rating scale, from "Never" to "Very Often" (Cuenca-Royo *et al*., 2012; Fernandez-Artamendi *et al*., 2012). The scores from each item are then totaled to give an overall score (Cuenca-Royo *et al*., 2012; Fernandez-Artamendi *et al*., 2012). This score helps to indicate the risk level for a substance use disorder, with higher scores suggesting a greater risk (Cuenca-Royo *et al*., 2012; Fernandez-Artamendi *et al*., 2012). Due to the fact that the study was conducted in Spain, the validated Spanish version was used.

Severity of Dependence Scale

The SDS is a self-administered, five-item questionnaire designed to measure the severity of dependence on drugs (Castillo *et al*., 2010; Cuenca-Royo *et al*., 2012). It assesses psychological dependence, compulsive use, and concerns about drug taking and control over drug use (Castillo *et al*., 2010; Cuenca-Royo *et al*., 2012). Each question is scored from 0 to 3, with higher scores indicating greater levels of dependence (Castillo *et al*., 2010; Cuenca-Royo *et al*., 2012). A total score of 5 or more suggests psychological dependence (Castillo *et al*., 2010; Cuenca-Royo *et al*., 2012). The SDS is widely used in both clinical and research settings to help understand the extent of an individual's drug dependence and to guide treatment decisions (Castillo *et al*., 2010; Cuenca-Royo *et al*., 2012).

Clinical Global Impressions scales

The CGI scales are widely used tools in clinical research and practice for assessing the severity of a patient's illness and their response to treatment (Busner & Targum, 2007). They are rated on a 7-point scale, where the clinician rates either the severity (CGI-S) of the patient's illness at the time of assessment; or their improvement (CGI-I) or worsening relative to the baseline state at the beginning of the intervention (Busner & Targum, 2007). The scale values range from 1 ("Very much worse") to 7 ("Among the most extremely ill patients") and 1 ("Very much improved") to 7 ("Very much worse") (Busner & Targum, 2007). The clinician's rating is based on their total clinical experience with the patient's diagnosis (Busner & Targum, 2007). Both scales are designed to be simple yet flexible, providing a quick and clinician-rated measure that reflects the patient's current treatment status and overall change (Busner & Targum, 2007).

Sheehan Disability Inventory

The SDI, also known as the Sheehan Disability Scale (SDS), is a self-report tool developed to assess functional impairment in three interrelated domains: work/school, social life, and family life (Bobes *et al*., 1999). Patients rate their impairment on a 10-point visual analog scale, with 0 indicating no impairment and 10 indicating severe impairment (Bobes *et al*., 1999). The scale uses spatio-visual, numeric, and verbal descriptive anchors to assist individuals in rating their impairment (Bobes *et al*., 1999). The scores from the three domains can be summed to create a single measure of global functional impairment, ranging from 0 (unimpaired) to 30 (highly impaired) (Bobes *et al*., 1999). Scores of 5 or greater on any of the scales are associated with significant functional impairment (Bobes *et al*., 1999).

Finally, sociodemographic parameters such as sex, age, marital status, educational level, and employment status; as well as course specifiers of schizophrenia (according to DSM-5) (American Psychiatric Association, 2013), pharmacological and psychotherapeutic therapies, hospital admissions, and relevant comorbidities were collected. Safety aspects were collected according to standard clinical practice but are out of scope for the present study.

Statistical analyses

Patient characteristics were summarized using descriptive statistics in percentages, means, and standard deviations. Least squares mean changes and effect sizes were calculated for the change from treatment start to treatment end for PANSS, CGI-SCH, CAST, SDS, SDI, CGI-S, and CGI-I using a mixed model for repeated measures. All analyses were conducted using Statistical Analysis System (SAS Institute, Cary, North Carolina, USA).

Results

Patient characteristics

Baseline patient characteristics are summarized in Table 1. Overall, 58 patients (no screening failures were registered) with schizophrenia and CUD were included in this observational study. The mean age was 34.2 years and 67.2% were men. Most patients were unmarried (56.9%), had low level of education (primary education 51.7%) and were unemployed (55.1%). Most of the cohort was diagnosed with schizophrenia with multiple episodes (62.1%), although first episode patients were also numerous (31.0%). Most patients had moderate or severe CUD at the beginning of treatment (86.2%). Additionally, patients exhibited different somatic comorbidities as well (27.6%).

Treatments

All patients were on cariprazine treatment as per inclusion criteria. The most frequent doses of cariprazine at the beginning of treatment were 4.5 mg/day (53.4%), followed by 3.0 mg/day (24.1%) (Table 2). Among these patients, 70.7% of them received additional non-pharmacological treatment, including psychotherapy. Other psychopharmacological treatments were also utilized such as antidepressants (50.0%), antipsychotics other than cariprazine (44.8%), antiepileptics (31.0%),

Table 1 Patient characteristics

Population	
Dual disorder patients, *n* (%)	58 (100)
Demographics	
Age, mean (SD), years	34.2 (9.5)
Males, *n* (%)	39 (67.2)
Marital status, *n* (%)	
Never been married	33 (56.9)
Living with partner	9 (15.5)
Married	6 (10.3)
Separated	9 (15.5)
Widowed	1 (1.7)
Educational level, *n* (%)	
Primary education	30 (51.7)
Secondary education	13 (22.4)
University studies	13 (22.4)
No studies	2 (3.5)
Employment status, *n* (%)	
Unemployed due to health reasons	18 (31.0)
Unemployed due to other reasons	14 (24.1)
Employed	9 (15.5)
Self-employed	9 (15.5)
Non-remunerated job	4 (6.9)
Student	3 (5.2)
Responsible for household chores	1 (1.7)
Schizophrenia characteristics	
Schizophrenia first episode, *n* (%)	18 (31.0)
Acute	5 (8.6)
Partial remission	7 (12.1)
Total remission	6 (10.3)
Schizophrenia multiple episodes, *n* (%)	36 (62.1)
Acute	13 (22.4)
Partial remission	15 (25.9)
Total remission	8 (13.8)
Schizophrenia continuous episodes	3 (5.2)
Non-specified episode	1 (1.7)
Cannabis use disorder characteristics	
Severity, *n* (%)	
Severe	22 (37.9)
Moderate	28 (48.3)
Mild	8 (13.8)
Remission, *n* (%)	
No remission	34 (58.6)
<3-month remission	11 (19.0)
Early remission (3–12 months)	11 (19.0)
Sustained remission (>12 months)	2 (3.4)
Restricted access to cannabis	17 (29.3)
Comorbidities	
Somatic comorbidity, *n* (%)	16 (27.6)
Hepatitis	5 (8.6)
Type 2 diabetes mellitus	4 (6.9)
Obesity	4 (6.9)
HIV	3 (5.2)
Arterial hypertension	2 (3.4)
Other	3 (5.2)

Table 2 Treatment characteristics

	Treatment start (*n* = 58)	Treatment end (*n* = 58)
Cariprazine therapy, *n* (%)	58 (100)	58 (100)
1.5 mg/ day	5 (8.6)	4 (6.9)
3.0 mg/day	14 (24.1)	13 (22.4)
4.5 mg/day	31 (53.4)	25 (43.1)
6.0 mg/day	6 (10.3)	15 (25.9)
Other pharmacotherapies		
Antidepressant	29 (50.0)	31 (53.4)
Benzodiazepines	16 (27.6)	13 (22.4)
Antipsychotics	26 (44.8)	24 (41.4)
Aripiprazole	2 (3.5)	2 (3.5)
Aripiprazole + Olanzapine	1 (1.7)	0 (0.0)
Clotiapine	2 (3.5)	0 (0.0)
Olanzapine	7 (12.0)	8 (13.8)
Paliperidone	5 (8.6)	5 (8.6)
Quetiapine	7 (12.0)	7 (12.0)
Tiapride	2 (3.5)	2 (3.5)
Antiepileptics	18 (31.0)	18 (31.0)
Alcohol interdictors	4 (6.9)	6 (10.3)
Opioid agonists	5 (8.6)	3 (5.2)
Non-pharmacological therapy	41 (70.7)	41 (70.7)

and benzodiazepines (27.6%) (see Table 2). By the end of the observational periods, there were some slight changes in the dosing of cariprazine (4.5 mg/day 43.1%, 6.0 mg/day 25.9%, 3.0 mg/day 22.4%, and 1.5 mg/day 6.9%). No change was detected in the number of patients receiving non-pharmacological therapy. In terms of other pharmacotherapies, there was no significant change either.

Substance use characteristics

Besides cannabis, the consumption of other substances was also tracked throughout the observational period. At the beginning of cariprazine treatment, 82.8% of patients used cannabis actively (Table 3). In addition, tobacco (51.7%), alcohol (27.6%), and cocaine (15.5%) were also consumed by some patients. By the end of the observational period, only 48.3% reported to consume cannabis, 55.2% smoked tobacco, 10.3% consumed alcohol, and only 1.7% used cocaine. On the other hand, 30 patients (51.7%) were not active cannabis users at the end of the study (Table 4). Among these, 12 patients (20.7%) were in precocious remission (<3 months), another 12 patients (20.7%) in early remission (3–12 months), and 6 patients (10.3%) in sustained remission (>12 months).

Effectiveness analyses

Effectiveness outcomes are presented in Table 5. The least squares mean change from beginning to end of treatment in the PANSS total score was –47.88 points ($P < 0.0001$, effect size: –3.0). PANSS Marder factor scores were also statistically significant at the end of treatment (6-month treatment period) with most improvements detected in the positive (least squares mean change: –13.09, $P < 0.0001$, effect size: –2.6) and negative (least squares mean change: –11.88, $P < 0.0001$, effect size: –3.3) factor score (Fig. 1). The least squares mean change from beginning to end of treatment in the CGI-SCH scores was –8.26 points ($P < 0.0001$, effect size: –2.9). Interestingly, most change according to this scale was detected in cognitive (least squares mean change: –1.73, $P < 0.0001$, effect size: –2.7) and positive (least squares mean change: –1.70, $P < 0.0001$, effect size: –2.3) symptoms (Fig. 2). Overall, patients improved from moderate-marked severity to mild overall severity according to the CGI-S scale (least squares mean change: –1.38, $P < 0.0001$, effect size: –2.7). In terms of change in substance use, the least squares mean change from beginning to end of treatment in the CAST total score was –7.0 points ($P < 0.0001$, effect size: –1.6). Furthermore, statistically significant effects were observed on the SDS; the least squares mean change from beginning

Table 3 Substance consumption

	Treatment start ($n = 58$)	Treatment end ($n = 58$)
Tobacco	30 (51.7)	32 (55.2)
Alcohol	16 (27.6)	6 (10.3)
Caffeine	3 (5.2)	1 (1.7)
Cannabis	48 (82.8)	28 (48.3)
Hallucinogens	1 (1.7)	1 (1.7)
Heroin	2 (3.4)	3 (5.2)
Sedatives	3 (5.2)	2 (3.4)
Cocaine	9 (15.5)	1 (1.7)

Table 4 Cannabis consumption at the end of the study

	n (%)
Cannabis consumption	28 (48.3)
No cannabis consumption	30 (51.7)
Precocious remission (<3 months)	12 (20.7)
Early remission (3–12 months)	12 (20.7)
Sustained remission (>12 months)	6 (10.3)

to end of treatment in the SDS total score was −7.88 ($P < 0.0001$, effect size: −2.2). Statistical significance was also reached in the SDI scale (least squares mean change: −9.48, $P < 0.0001$, effect size: −1.8), especially in family life (least squares mean change: −2.74, $P < 0.0001$, effect size: −1.8) and perceived stress (least squares mean change: −2.54, $P < 0.0001$, effect size: −1.9).

Discussion

The aim of this 6-month observational study was to evaluate the antipsychotic effectiveness of cariprazine in 58 patients with a dual disorder of schizophrenia and CUD in a real-world setting. Cariprazine was effective in addressing overall symptoms of schizophrenia as measured by the PANSS and the CGI-SCH. Symptoms of CUD also improved, as shown by an improvement on the CAST and SDS scales. Improvement was also seen on the CGI global scale and SDI.

The findings of this study are in line with those of earlier controlled clinical trials, showing substantial decreases in both the PANSS and CGI scores (Durgam *et al*., 2014, 2015, 2016; Kane *et al*., 2015). Additionally, functional improvement observed in the present study with the SDI is also in line with improvements previously recorded with the Personal and Social Performance Scale (Marder *et al*., 1997; Durgam *et al*., 2016; Németh *et al*., 2017). Improvement in day-to-day functioning is a crucial aim in schizophrenia treatment, as it impacts quality of life, adherence, and overall satisfaction with treatment (Leijala *et al*., 2021).

Concerning CUD, to our best knowledge, this is the first structured study to examine cariprazine's efficacy in this patient population. Present study results are in line with previous case reports (Sanders & Miller, 2019; Montes *et al*., 2021; Rodriguez Cruz *et al*., 2021; Gentile *et al*., 2022), and a literature-based study (Martinotti *et al*., 2022) suggesting that cariprazine might have beneficial

Table 5 Effectiveness of treatment

	Treatment start Mean (SD)	Treatment end Mean (SD)	Least squares mean change (SE)	Effect size
PANSS total	114.4 (31.4)	66.5 (25.2)	−47.88*** (2.55)	−3.0
Positive factor score	30.7 (8.7)	17.6 (7.7)	−13.09*** (0.79)	−2.6
Negative factor score	28.9 (7.5)	17.0 (5.5)	−11.88*** (0.59)	−3.3
Cognitive factor score	19.1 (5.9)	10.6 (4.7)	−8.50*** (0.52)	−2.6
Hostility/Excitement factor score	18.0 (6.6)	10.4 (5.1)	−7.67*** (0.45)	−2.8
Depression/Anxiety factor score	15.3 (5.4)	9.2 (3.7)	−6.05*** (0.32)	−2.8
CGI-SCH	20.8 (5.4)	12.6 (4.1)	−8.26*** (0.49)	−2.9
Positive symptoms	4.2 (1.3)	2.5 (1.2)	−1.70*** (0.13)	−2.3
Negative symptoms	4.1 (1.3)	2.6 (0.8)	−1.53*** (0.10)	−2.8
Depressive symptoms	4.0 (1.4)	2.5 (1.0)	−1.51*** (0.11)	−2.1
Cognitive symptoms	4.1 (1.2)	2.3 (0.9)	−1.73*** (0.11)	−2.7
Global severity	4.5 (1.2)	2.6 (0.9)	−1.83*** (0.11)	−2.8
CGI-I	3.7 (1.8)	1.7 (0.9)	−2.26*** (0.12)	−2.4
CGI-S	4.6 (0.9)	3.2 (0.7)	−1.38*** (0.09)	−2.7
SDI total	24.8 (7.3)	15.3 (8.1)	−9.48*** (0.92)	−1.8
Work	6.4 (1.9)	4.4 (2.4)	−1.98*** (0.27)	−1.4
Social life	6.2 (2.1)	3.8 (2.1)	−2.31*** (0.25)	−1.6
Family life	6.3 (2.2)	3.6 (2.2)	−2.74*** (0.27)	−1.8
Perceived stress	6.0 (2.1)	3.5 (2.0)	−2.54*** (0.24)	−1.9
Perceived social support	–	–	–	–
CAST	21.4 (3.3)	14.4 (6.5)	−7.00*** (0.82)	−1.6
SDS	14.6 (8.5)	6.8 (5.4)	−7.88*** (0.60)	−2.2

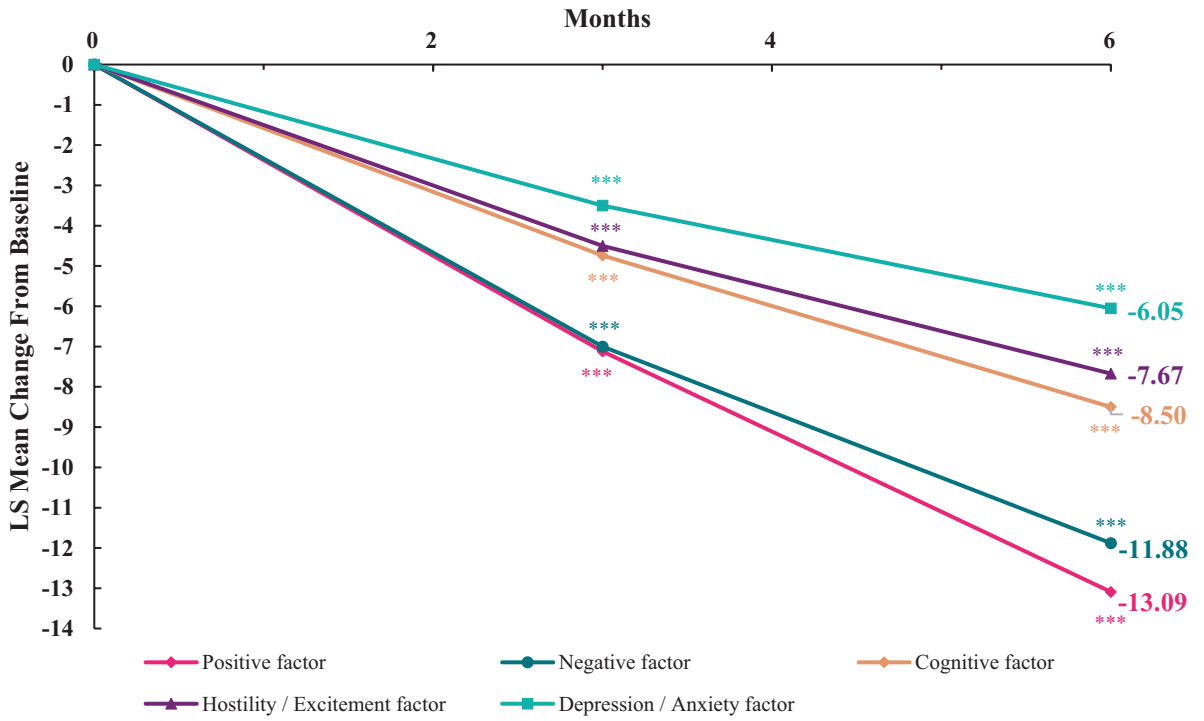
CAST, Cannabis Abuse Screening Test; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity; CGI-SCH, Clinical Global Impression-Schizophrenia, PANSS, Positive and Negative Syndrome Scale; SDI, Sheehan Disability Inventory; SDS, Severity of Dependence Scale; SE, standard error.

* *P*-value <0.05.

*** *P*-value <0.0001.

effects in addressing this disorder. Current dual disorder guidelines (Martinotti *et al*., 2022; Szerman *et al*., 2022) suggest the use of second-generation antipsychotics, and among these, dopamine partial agonists have emerged as having benefits. While studies have cited the efficacy of aripiprazole (Szerman *et al*., 2020) and brexpiprazole (Kung *et al*., 2022; Chiappini *et al*., 2024) in dual schizophrenia patients with different substance use disorders, cariprazine differentiates from these two partial agonists by having a preferential binding (Stahl, 2017; Grunze *et al*., 2021) to the D3 receptors, a quality that might bring additional benefits in addressing substance use. The D3 has been described to play a pivotal role in reward-related behaviors (Kiss *et al*., 2010; Leggio *et al*., 2013, 2016; Cortés *et al*., 2016) and repeated administration of substances causes an upregulation in these receptors, while D2 receptors are downregulated (Galaj *et al*., 2020). Hence, with repeated substance use, D3 receptors become more prevalent (upregulated), potentially making the brain more responsive to dopamine in certain pathways, while D2 receptors become less prevalent (downregulated) (Galaj *et al*., 2020). Blocking the D2 receptors under these conditions might not have the same impact as targeting the upregulated D3 receptors (Galaj *et al*., 2020). Hence, agents with D3 blocking activity such

Fig. 1



Change from treatment start to end in PANSS total and factor scores. PANSS, Positive and Negative Syndrome Scale.

as cariprazine might have advantages due to higher selectivity, improved pharmacokinetic profiles, enhanced opioid analgesia, and minimal side effects (Galaj *et al.*, 2020).

In this study, additional improvements were seen in reducing cocaine and alcohol abuse with cariprazine treatment. These findings are again in line with smaller case reports describing improvement in a mental health disorder and comorbid cocaine (Carmassi *et al.*, 2019; Vannucchi *et al.*, 2022) and alcohol (Carmassi *et al.*, 2019) use disorder. Interestingly, cariprazine treatment did not result in any significant reduction in tobacco use, which is a highly prevalent comorbidity among patients with schizophrenia. According to the literature, nicotine may improve hyperconnectivity in patients with schizophrenia (Ward *et al.*, 2022) by targeting the cholinergic/nicotinic system and hence explain why tobacco use did not improve with cariprazine [no action on these receptors (Kiss *et al.*, 2010)].

This study is not without limitations. First, the study has a modest sample size and an absence of controls which inherently limit the conclusions. Secondly, we included patients with the dual diagnosis of schizophrenia and CUD according to DSM-5; and cannot exclude that patients who initially got a diagnosis of substance-induced psychosis and then later transitioned to schizophrenia and substance-used disorder were also included. Additionally, for assessing substance use, only self-reported questionnaires were used – physician-based scales or verifying laboratory tests were not performed – which might result in reporting bias. Further studies, with double blind, controlled designs are needed to validate these findings.

Conclusion

The study has shown beneficial effects of cariprazine on overall symptoms of schizophrenia along with improvements in self-reported CUD. Further well-designed studies are needed to validate these findings.

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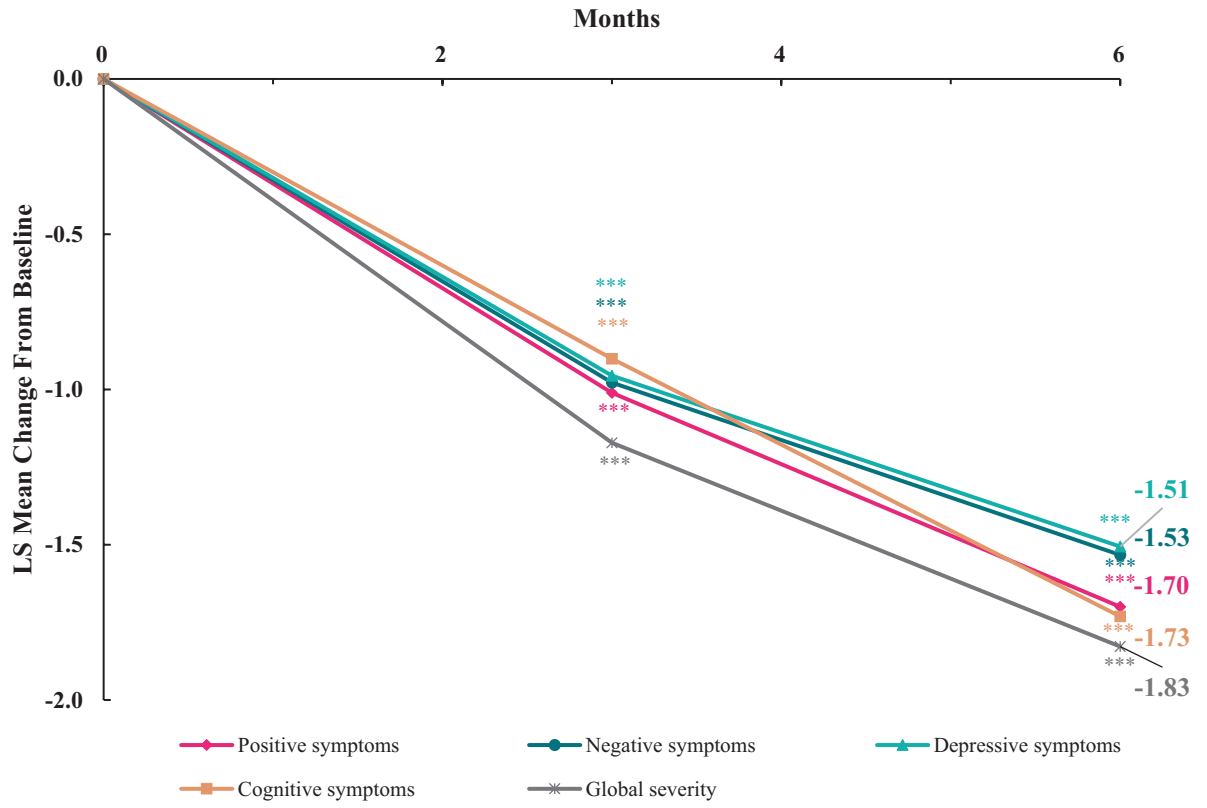
The study received ethics approval from the Ethics Research Committee at the Gregorio Marañón University Hospital in Madrid (FPD-CAR-2021-01) and informed written consent was obtained from all participants. The guidelines set by the Declaration of Helsinki were followed.

The datasets analyzed for this study are available from the corresponding author upon a reasonable request.

Conflicts of interest

There are no conflicts of interest.

Fig. 2



Change from treatment start to end in CGI-SCH. CGI-SCH, Clinical Global Impression-Schizophrenia

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